IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	CVITKOVICH et al.	Confirmation No.:	9636
Serial No.:	09/787,461	Examiner:	SPIVACK, Phyllis G
Filed:	March 2, 2001	Group Art Unit:	1614
For:	COMPOSITIONS AND USES OF ET 743 FOR TREATING CANCER		

DECLARATION OF JOSE JIMENO UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jose Jimeno, hereby declare that:

1. I am a co-inventor of the subject matter claimed in United States Patent Application Serial No. 09/787,461 ("the '461 application").

2. I am a citizen of Spain and an employee of Pharma Mar, S.A., the assignee of the entire right, title, and interest in the '461 application.

3. I have been employed by Pharma Mar, S.A. for 13 years, first as Vice President of Clinical R&D and since 2002 as Vice President of Scientific Development.

4. I have read and am familiar with the disclosure of published PCT application WO 00/69441, which published on November 23, 2000, from application number

PCT/GB00/01857, filed May 15, 2000. The '461 application is the entry of the national phase in the United States of PCT/GB00/01857.

5. I have read the February 27, 2007, non-final Office Action issued by the U.S. Patent and Trademark Office in the above-identified application, in which the Examiner rejected pending claims 12-17 and 24-35 under 35 U.S.C. §103(a) for "being unpatentable over both Taamma et al., Eur. J. Cancer, and Cvitkovic et al., ASCO Meeting held May 17, 1999, Abstract published in Clinical Cancer Research and on-line at www.asco.org., in view of Goodman & Gilman" as noted on page 5 of the Office Action.

6. "Cvitkovic et al., ASCO Meeting held May 17, 1999, Abstract published in Clinical Cancer Research and on-line at www.asco.org.," ("the Cvitkovic reference") as cited in the Office Action refers to the reference attached following my signature. I believe the ASCO Meeting cited for the Cvitkovic reference was held May 15-17, 1999.

7. The listed co-authors for the Cvitkovic reference are E. Cvitkovic, M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, J. M. Jimeno, B. Mekranter, C. Guzman, E. Brain, and J. L. Misset.

8. The listed co-inventors for the '461 application are Esteban Cvitkovic, George Daniel Demetri, Cecilia Guzman, Jose Jimeno, Luis Lopez Lazaro, Jean Louis Misset, Chris Twelves, and Daniel D. Von Hoff.

9. I am a co-author of the Cvitkovic reference (listed as J. M. Jimeno) as well as being a co-inventor of the '461 application. In addition, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset are listed as both co-authors of the Cvitkovic reference and co-inventors of the '461 application.

10. The listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application are M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain.

11. The listed co-authors M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, B. Mekranter, and E. Brain were medical fellows in a hospital working under the supervision of Esteban Cvitkovic and/or Jean Louis Misset. The listed co-author J. Beijnen performed physical analysis of samples under the supervision of Luis Lopez Lazaro.

12. The subject matter of the Cvitkovic reference relied upon by the Office Action is as follows:

> Cvitkovic teaches a dosage range of 50-1800 mg/m^2 to be administered as an infusion over 24 hours every 3 weeks. The number of cycles taught is 1-8 with 2 being the median number. As required by claim 30, Cvitkovic includes such tumor types as colorectal, sarcoma, breast, ovary, renal, bladder, gastric, ACUP, larynx, melanoma and osteosarcoma. As required by claims 31 and 32, one partial response was seen in a patient with metastatic breast cancer refractory to anthracycline and docetaxel, and another partial response was observed in a heavily pretreated patient with metastatic osteosarcoma.

(see Office Action, page 5, line 20 through page 6, line 2).

13. The listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at the dosage range of 50-1800 mg/m^2 to be administered as an infusion over 24 hours every 3 weeks or were working under the direction of one or more of the listed co-authors/co-inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at such subject matter.

14. The listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at the number of cycles of 1-8 with 2 being the median number or were working under the direction of one or more of the listed co-authors/co-inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at such subject matter.

15. The listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at tumor types selected from colorectal, sarcoma, breast, ovary, renal, bladder, gastric, ACUP, larynx, melanoma and osteosarcoma tumors or were working under the direction of one or more of the listed co-authors/co-inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at such subject matter.

16. The listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at observing one partial response in a patient with metastatic breast cancer refractory to anthracycline and docetaxel and observing another partial response in a heavily pretreated patient with metastatic osteosarcoma, or were working under the direction of one or more of the listed co-authors/co-inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at such subject matter.

17. In conclusion, the listed co-authors of the Cvitkovic reference who are not listed as co-inventors of the '461 application (M. Riofrio, F. Goldwasser, S. Delaloge, A. Taamma, J. Beijnen, B. Mekranter, and E. Brain) either did not arrive at the subject matter relied

upon in the Office Action or were working under the direction of one or more of the listed co-authors/co-inventors (Jose Jimeno, Esteban Cvitkovic, Cecilia Guzman, and Jean Louis Misset) in arriving at the subject matter cited in the Office Action.

18. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____ August 3, 2007
Jose Jimeno Date

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Final Results of a Phase I Study of Ecteinascidin-743 (ET-743) 24 Hour (h) Continuous Infusion (CI) in Advanced Solid Tumors (AST) Patients (pts) (Meeting abstract).

Sub-category: Clinical Pharmacology
Category: Clinical Pharmacology
Meeting: 1999 ASCO Annual Meeting

Abstract No: 600

Author(s): E Cvitkovic, M Riofrio, F Goldwasser, S Delaloge, A Taamma, J Beijnen, JM Jimeno, B Mekranter, C Guzman, E Brain, JL Misset

Abstract: ET-743 is a novel minor groove DNA binding agent specific to guanine-cytosine rich regions with activity in murine tumor models and human cancer xenografts. Bone marrow and hepatic toxicities were dose limiting in animals. The results of phase I study with ET-743 CI 24 h given every 3 weeks, in AST pts are presented. Between 5/96 and 11/98, 49 pts received a total of 148 cycles (cy) over 9 dose levels (DL) (50--1800 mg/m[Superscript 2]), median number of cy/pts = 2 (1--8). Median age 59 (19--75) F/M = 28/21, median ECOG PS 1 (1--2). Tumor types: Colorectal (12), sarcoma (11), breast (7), ovary (6), renal (3), bladder (2), gastric (2), ACUP (2), larynx (1), melanoma (1), 2 pts had both sarcoma and breast cancer. Acute nausea/vomiting (grade 2) were seen from the 600 mg/m[Superscript 2] DL. Emesis was easily controlled. Reversible transaminases elevation peaking at days 3--7, back to baseline by day 14 occurred at the 4 highest DL and was never a Dose Limiting Toxicity (DLT). The Maximal Tolerated Dose was 1800 mg/m[Superscript 2], with neutropenia and thrombopenia being the DLTs. The Recommended Dose for phase II studies is 1500 mg/m[Superscript 2]. The table below summarize the severe toxicities (NCI-CTC) by pts and cy observed at the 4 highest DLs: One partial response (PR) was seen in pt with metastatic breast cancer refractory to anthracycline and docetaxel, another PR was observed in a heavily pretreated pt with metastatic osteosarcoma, with several minor and biological responses also seen in breast, sarcoma and colon, all in pts receiving doses >=1200 mg/m[Superscript 2]. Phase II trials with ET-743 are warranted. Since treatment is ongoing in 6 pts, final results with all evaluable cy will be presented. PK/PD relationships are presented elsewhere.

Other Abstracts in this Sub-Category

1. **The Farnesyl Protein Transferase (FPTase) Inhibitor L-778,123 in Patients with Solid Cancers (Meeting abstract).**
   Meeting: 1999 ASCO Annual Meeting Abstract No: 597 First Author: CD Britten
   Category: Clinical Pharmacology
2. **A Phase I and Pharmacologic Study of the Farnesyl Protein Transferase (FPT) Inhibitor SCH 66336 in Patients with Locally Advanced or Metastatic Cancer. (Meeting abstract).**
   Meeting: 1999 ASCO Annual Meeting Abstract No: 598 First Author: Adjei Alex
   Category: Clinical Pharmacology
3. **Phase I and Pharmacokinetic Study of SCH66336, a Novel FPTI, Using a 2-Week on, 2-week off Schedule. (Meeting abstract).**
   Meeting: 1999 ASCO Annual Meeting Abstract No: 599 First Author: Hurwitz Herbert
   Category: Clinical Pharmacology

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Abstracts by E Cvitkovic

1. **Phase II trial of oxaliplatin and paclitaxel combination in advanced ovarian cancer patients pretreated with cisplatin or carboplatin ƒ taxanes: preliminary results**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 891 First Author: P Viens
   Category: Gynecologic Cancer
2. **Chronomodulated (CRM) Bimonthly 48 Hour (Hr) 5-Fluorouracil (FU), Folinic Acid (FA), Oxaliplatin (OXA)**

'FOLFOX CRM' in FU-Refractory (FUR) Advanced Colorectal Cancer (ACRC) Patients (Pts): Phase II Study.
Meeting: 2000 ASCO Annual Meeting Abstract No: 1242 First Author: Frédérique Penault-Cvitkovic
Category: Gastrointestinal Cancer

3. Ecteinascidin-743 (ET-743) in Taxane (T)/Anthracycline (A) Pretreated Advanced/Metastatic Breast Cancer (A/MBC) Patients (Pts): Preliminary Results with the 24 Hour (H) Continuous Infusion (CI) Q3week Schedule.
Meeting: 2000 ASCO Annual Meeting Abstract No: 592 First Author: Laurent Zelek
Category: Breast Cancer

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Journal of Clinical Oncology Articles by E Cvitkovic

1. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients.
J Clin Oncol, United States
Vol 22, No 5 (Mar 1, 2004): pp. 890-9
2. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients.
J Clin Oncol, United States
Vol 20, No 23 (Dec 1, 2002): pp. 4543-8
3. Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study.
J Clin Oncol, United States
Vol 20, No 6 (Mar 15, 2002): pp. 1512-8
4. Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors.
J Clin Oncol, United States
Vol 19, No 5 (Mar 1, 2001): pp. 1256-66
5. Ecteinascidin-743: a marine-derived compound in advanced, pretreated sarcoma patients--preliminary evidence of activity.
J Clin Oncol, United States
Vol 19, No 5 (Mar 1, 2001): pp. 1248-55
6. Phase I/II study of escalating doses of vinorelbine in combination with oxaliplatin in patients with advanced non-small-cell lung cancer.
J Clin Oncol, United States
Vol 19, No 2 (Jan 15, 2001): pp. 456-63
7. Long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type.
J Clin Oncol, UNITED STATES
Vol 18, No 6 (Mar, 2000): pp. 1324-30
8. Factors predicting for efficacy and safety of docetaxel in a compassionate-use cohort of 825 heavily pretreated advanced breast cancer patients.
J Clin Oncol, UNITED STATES
Vol 18, No 3 (Feb, 2000): pp. 582-73
9. Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent phase I studies with pharmacokinetics.
J Clin Oncol, UNITED STATES
Vol 17, No 6 (Jun, 1999): pp. 1751-9
10. Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment.
J Clin Oncol, UNITED STATES
Vol 16, No 8 (Aug, 1998): pp. 2746-51

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PubMed Articles by E Cvitkovic PubMed

1. Pharmacokinetics, Metabolism, and Routes of Excretion of Intravenous Irofulven in Patients with Advanced Solid Tumors.
Drug Metab Dispos,
Vol , No (8/10/2006): pp.
PMID: 16896064 [PubMed - in process]
2. A phase II study of an oxaliplatin/vinorelbine/5-fluorouracil combination in patients with anthracycline-pretreated and taxane-pretreated metastatic breast cancer.
Anticancer Drugs,
Vol 17, No 9 (9/27/2006): pp. 1067-1073
PMID: 17001160 [PubMed - in process]
3. Repression of cell cycle-related proteins by oxaliplatin but not cisplatin in human colon cancer cells.
Mol Cancer Ther, United States

Vol 5, No 9 (9/21/2006): pp. 2149-57
PMID: 16985047 [PubMed - in process]
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